Omega-6 Fatty Acids

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Biomarkers for Diet and Chronic Diseases

Xin Huang and Jie V. Zhao

Contents

Abstract

Omega-6 fatty acids are involved in a series of biological processes including inflammation, immune function, and carcinogenesis. Omega-6 fatty acids are closely related to multiple chronic diseases, such as cardiovascular disease, diabetes, asthma, autoimmune diseases, and cancer, however, the evidence is controversial. Omega-6 fatty acids are also responsive to dietary intake and therefore serve as biomarkers for dietary intake. This chapter provides a narrative review of omega-6 fatty acids as biomarkers for major chronic diseases, summarizes the usefulness and limitations of omega-6 fatty acids as biomarkers in epidemiological research and clinical applications, with implicatoins for using omega-6 fatty acids as biomarkers for disease prediction, dietary interventions and primary health care.

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Keywords

Omega-6 fatty acids · Diet · Cardiovascular disease · Diabetes · Asthma · Autoimmune disease · Cancer

Abbreviations

5-HETE	5 hydroxyeicosatetraenoic
AA	Arachidonic acid
CHD	Coronary heart disease
CVD	Cardiovascular disease
D5D	Delta-5-desaturase
D6D	Delta-6-desaturase
DGLA	Dihomo-γ-linolenic acid
GLA	γ-linolenic acid
IL	Interleukin
JIA	Juvenile idiopathic arthritis
LA	Linoleic acid
LT	Leukotrienes
LXA4	Lipoxin A4
MI	Myocardial infarction
MS	Multiple sclerosis
PUFAs	Polyunsaturated fatty acids
RA	Rheumatoid arthritis
SLE	Systemic lupus erythematosus
T2D	Type 2 diabetes
TNF-α	Tumor necrosis factor-α

Introduction

Omega-6 fatty acids (also known as n-6 fatty acids or ω-6 fatty acids) are a type of polyunsaturated fatty acids (PUFAs), where the final carbon-carbon double bond at the farthest end of the carboxyl group in the molecule is located on the sixth carbon atom counting from the methyl end (n-6). Linoleic acid (LA) and arachidonic acid (AA) are the most common omega-6 in diet, mainly derived from vegetable oils, cereals, red meat, poultry and so on. LA (18:2, n-6) is a precursor of AA (20:4, n-6), which can be converted into AA through γ-linolenic acid (GLA, 18:3, n-6) and dihomo-γ-linolenic acid (DGLA, 20:3, n-6) by desaturase and elongase enzymes (Fig. 1).

Omega-6 fatty acids are responsive to dietary intake, which can be used as biomarkers for diet. In addition, accumulating epidemiological studies suggest that omega-6 fatty acids are involved in the pathogenesis of multiple chronic diseases, such as cardiovascular disease, diabetes, asthma, autoimmune disease, cancer, etc., with the potential of being applied as biomarkers for these diseases. In this chapter, we provide a narrative review of omega-6 fatty acids as biomarkers for dietary

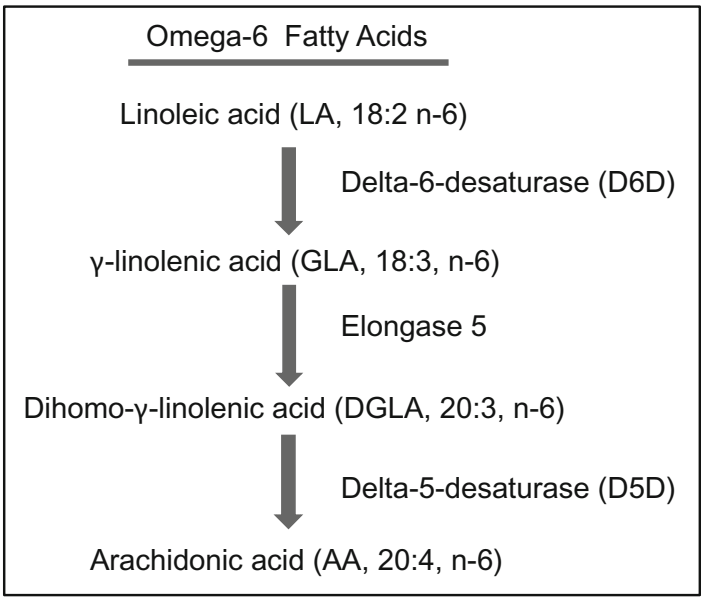

Fig. 1 Pathway of omega-6 fatty acids metabolism

intake and major chronic diseases, and summarize the potential and limitations of using omega-6 fatty acids as biomarkers in epidemiological research and clinical applications.

Omega-6 Fatty Acids as Biomarkers for Dietary Intake

Nutrition and diet are modifiable risk factors with the potential to prevent chronic diseases. In order to clarify the relationship between diet and diseases, dietary assessment has become a key issue. Most studies used the Food Frequency Questionnaires (FFQ) or 24-hour dietary recall as instruments to assess habitual dietary intake (Reigada et al. 2021). Although they are convenient to use in large epidemiological studies, they might be open to recall bias, for example, arising from incorrect estimation of portion sizes, and misclassification of food components (Kristal et al. 2005; Picó et al. 2019). Fat is often one of the most underestimated items in various dietary self-report surveys (Subar et al. 2003; Subar et al. 2001). To overcome the limitations, endogenous omega-6 fatty acids, responsive to dietary fat intake, can be used as biomarkers for dietary intake. In an intervention study conducted by Hodson et al. (2014), LA abundance was measured in participants during a intervention with diet enriched with omega-6 fatty acids; the percentage of total fatty acids in each lipid fraction (Plasma cholesterol ester, plasma phospholipid, plasma triglyceride, erythrocyte phospholipid, and buccal cell phospholipid) increased with LA during the first 2 weeks of the omega-6 diet period, suggesting

that changes in LA content can be used as a marker of dietary change. Baylin and Campos (2006) summarized the results of studies quantifying dietary compliance using fatty acids from plasma fractions and found a dose-response relationship with serum cholesterol ester LA following a gradual increase in LA intake. It is necessary to explore omega-6 biomarkers as alternative options for measuring dietary intake in epidemiological and clinical studies.

Assessment of omega-6 fatty acid biomarkers is readily accessible and diverse, using a variety of blood fractions, including total blood, plasma, serum, erythrocytes, as well as tissue sampling from adipose tissues. In most studies, blood fractions are more commonly used for biomarker measurements because they are easier to obtain and measure, compared to adipose tissues. Plasma and serum levels are considered to reflect short-term intake over a few days (Katan et al. 1997), while erythrocytes and adipose tissues are a better long-term marker due to the long half-life (Albert et al. 2002; Smedman et al. 1999) for example, 6 months to 2 years for LA in adipose tissue (Beynen et al. 1980; Hodson et al. 2014; Strawford et al. 2004). Experimental studies have also shown that adipose tissue can reflect dietary compliance within 5 years (Baylin and Campos 2006; Dayton et al. 1967). Total blood, plasma, serum, and erythrocytes all proved to be reliable in accessing fatty acid intake (Baylin et al. 2005; Hodson et al. 2014). The choice of measurement should take into account the cost of sample collection and preparation, as well as the objective of assessment.

Omega-6 Fatty Acids as Biomarkers for Cardiovascular Disease

Omega-6 fatty acids have long been believed to be related to cardiovascular diseases, and thus a potential biomarker for cardiovascular disease, while the evidence from different study designs is inconsistent. In case-control studies, serum and erythrocyte LA were lower in patients with coronary artery disease compared with controls (Block et al. 2008; Song et al. 2014). In contrast, serum AA were higher in patients than in healthy controls (Song et al. 2014). A meta-analysis of observational studies conducted by Harris et al. (2007) also showed that lower blood/tissue levels of LA were associated with an increased risk of CHD, while AA levels in adipose tissue were positively associated with CHD events. Marklund et al. (2019) conducted an individual-level meta-analysis in a global consortium of 30 prospective observational studies from 13 countries and found that higher in vivo circulating or tissue levels of LA were associated with lower risk of total CVD, cardiovascular mortality, and ischemic stroke, whereas AA was only weakly negatively associated with lower risk of total CVD. However, these observed beneficial associations have not been corroborated in randomized controlled trials (RCTs) and Mendelian randomization. Specifically, a recent systematic review and meta-analysis including 19 RCTs showed no clear benefit of omega-6 fatty acids on cardiovascular disease events and mortality (Hooper et al. 2018). Using Mendelian randomization to minimize confounding (Fig. 2), Zhao and Schooling (2019a) showed that genetically predicted endogenous LA

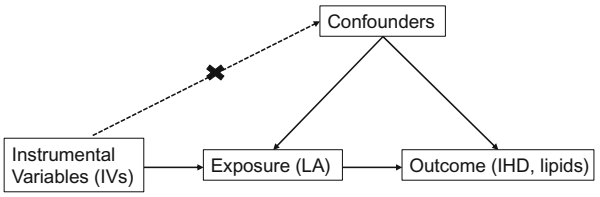

Fig. 2 Diagram of MR study

Table 1 Genetically predicted LA with IHD and lipids using Mendelian randomization

Exposure	Outcome	OR/ Beta	95% CI	P value
Linoleic acid (% in total fatty acids)	Ischemic heart disease (IHD)	1.01	0.95 to 1.08	0.71
	LDL cholesterol	− 0.032	− 0.037 to − 0.027	<0.001
	HDL cholesterol	− 0.026	− 0.031 to − 0.021	<0.001
	Total cholesterol	− 0.030	−0.035 to − 0.026	<0.001

From: Effect of linoleic acid on ischemic heart disease and its risk factors: a Mendelian randomization study

levels were inversely associated with lipids, but the association with CHD events was not significant (Table 1), which showed consistency with evidence from meta-analysis of RCTs.

Omega-6 Fatty Acids as Biomarkers for Diabetes

In addition to cardiovascular disease, omega-6 fatty acids are also relevant to diabetes. A systematic review and meta-analysis including 102 RCTs showed that compared to carbohydrate, saturated fatty acids and monounsaturated fatty acids, dietary polyunsaturated fatty acids (mainly LA) have beneficial effects on diabetes (Imamura et al. 2016). Wu et al. (2017) summarized the association of LA and LA biomarkers with incidence of T2D in 20 prospective cohort studies with a total of 39,740 participants, and showed that higher LA was associated with a lower risk of T2D, while the association was not observed for AA. In nested case-cohort studies from the European Prospective Investigation into Cancer (EPIC) cohort (15,919 participants), plasma LA was also inversely related to T2D, independent of AA (Forouhi et al. 2016).

Despite, Weir et al. (2020) proposed a new hypothesis that omega-6 fatty acids are more likely to be markers of hyperinsulinemia rather than protective or risk factors for T2D. Insulin may be the main driver of these associations by the mechanism that Insulin can stimulate D6D, leading to the conversion of LA to GLA, and then to DGLA. While stimulating D6D, increased long-chain PUFA will

inhibit D5D activity, resulting in reduced conversion of DGLA to AA (Arbo et al. 2011; Vessby et al. 2002). Consistently, after accounting for hyperinsulinemia, the association of T2D risk with LA, DGLA and AA was attenuated, suggesting that omega-6 fatty acids might be a marker of metabolic changes in pre-diabetes.

Omega-6 Fatty Acids as Biomarkers for Asthma

Asthma is a common respiratory disease characterized by chronic airway inflammation with the involvement of multiple cells (eosinophils, mast cells, T lymphocytes, neutrophils, etc.) and cellular components. Regulation of the inflammatory response is one of the important physiological functions of omega-6 fatty acids. Nested case-control studies in children showed that serum LA was associated with lower risk of asthma and better lung function (measured by FEV1), while AA levels were strongly associated with increased asthma prevalence and reduced FEV1 (Bolte et al. 2006). A case-control study analyzing erythrocyte membrane fatty acids in adults also reported that higher levels of membrane LA were associated with a lower risk of asthma (Broadfield et al. 2004). A Mendelian randomization study by Zhao and Schooling (2019b) also reported that genetically predicted higher LA was associated with a lower risk of asthma and lower levels of eosinophils and neutrophils (Table 2). In addition, corticosteroids are commonly used in clinical practice to treat asthma, and animal studies have shown that glucocorticoids could inhibit the release of AA from phospholipids and that any pharmacological effect of corticosteroids may lead to increased levels of LA in asthma patients (Blackwell et al. 1980). Therefore, changes in LA or AA levels may be of clinical value as a biomarker to guide medication in patients with asthma.

There are several possible explanations. LA may act through the derivatives PGE2 and LXA4 (Bonnans et al. 2002; Sastre and del Pozo 2012), which can inhibit

Table 2 Genetically predicted LA with asthma and white blood cell traits using Mendelian randomization

Exposure	Outcome	Source	OR/ Beta	95% CI	P value
Genetically predicted LA	Asthma	TAGC	0.70	0.58 to 0.83	6.8×10^{-5}
		UK Biobank	0.73	0.64 to 0.84	2.9×10^{-6}
		Both	0.72	0.65 to 0.80	1.2×10^{-9}
	Eosinophilic count	UK Biobank	−0.03	−0.061 to −0.004	0.02
	Neutrophil count	UK Biobank	−0.04	−0.057 to −0.023	3.6×10^{-6}
	Monocyte count	UK Biobank	−0.02	−0.046 to 0.008	0.16

From: The role of linoleic acid in asthma and inflammatory markers: a Mendelian randomization study

the proliferation of T helper cells and the production of various cytokines, such as IL-1, IL-2, and TNF-α, suppress the aggregation of pro-inflammatory cytokines and inflammatory cell, thus suppressing the airway inflammatory response (Namazi 2004). LA also has the potential to suppress asthma by increasing androgenic activity and promoting immune senescence (Gromadzka-Ostrowska 2006), as sex hormones have been shown to be beneficially associated with asthma (Scott et al. 2016). In addition, the conversion of LA to AA may be enhanced in asthma patients (Bolte et al. 2006). As a precursor of prostaglandin D2, AA contributes to and increases the production of pro-inflammatory cytokines and leukotrienes (Fajt et al. 2013), which leading to bronchoconstriction, increased vascular permeability and mucus secretion, and additional release of pro-inflammatory cytokines (Funk 2001). Patients with asthma have elevated circulating or tissue levels of AA and decreased levels of LA, reflecting ongoing airway inflammation, suggesting that omega-6 may serve as a potential predictive or diagnostic biomarker for asthma.

Omega-6 Fatty Acids as Biomarkers for Autoimmune Disease

Omega-6 fatty acids may also be used to predict common autoimmune disease, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), multiple and sclerosis (MS). A metabolomics study comparing serum metabolites in 20 SLE patients and 9 healthy controls found that serum omega-6 fatty acid (LA, GLA, DGLA, and dihomolinoleate) were significantly lower in SLE patients than in controls (Wu et al. 2012). A case-control study of juvenile idiopathic arthritis (JIA) found no significant difference in dietary intake of omega-6 fatty acids between patients and controls, but serum AA levels were lower in patients, especially in patients with active and short-lasting disease, and serum total omega-6, LA, and AA levels were inversely correlated with the number of active joints, suggesting a protective association against JIA (Gorczyca et al. 2017). For rheumatoid arthritis (RA), de Pablo et al. (2018) conducted a nested case-control study in recent years and found that high erythrocyte levels of omega-6 fatty acid LA were associated with a reduced risk of RA in southern European. A Mendelian randomization study conducted by Zhao and Schooling (2019c) also found that genetically predicted LA was associated with lower risk of RA and SLE (Table 3). As such, omega-6 fatty

Table 3 Genetically predicted LA with RA and SLE using Mendelian randomization

Exposure	Outcome	Source	OR	95% CI	P value
Genetically predicted LA	RA	Rheumatoid Arthritis Consortium	0.96	0.94–0.98	<0.001
		Meta-analysis with UK Biobank	0.97	0.95–0.98	<0.001
	SLE	ImmunoBase Consortium	0.95	0.91–0.99	0.02
		Meta-analysis with UK Biobank	0.95	0.92–0.99	0.01

From: Role of linoleic acid in autoimmune disorders: a Mendelian randomization study

acids may predict SLE and RA. Their role in MA is less clear. RCTs did not show any beneficial effects of dietary supplementation with omega-6 fatty acids on relapse rates, disability progression, or disease activity in clinically active MS (Wergeland et al. 2012).

Omega-6 Fatty Acids as Biomarkers for Cancer

Cancer is the leading cause of global morbidity and mortality. The most common cancers include lung, breast, intestinal, and prostate cancers, accounting for 40% of diagnosed cancers in the world (https://www.cancerresearchuk.org/health-professional/cancer-statistics/worldwide-cancer#heading-One (2019)). In vitro and in vivo animal studies have shown that AA might involve in cancer pathology (Sauer et al. 2007; Xu and Qian 2014), such as the proliferation of human breast cancer cell line BT-474 and lung cancer cell line A549 (Mouradian et al. 2014; Welsch 1992). In contrast, GLA, the derivative of LA, can inhibit the cell growth in vitro of human neuroblastoma cell lines and others (Fujiwara et al. 1986), selectively induce apoptosis in multiple human cancer cell lines including human breast cancer cells, lung cancer cells, and prostate cancer cells (Xu and Qian 2014), and dietary supplements of GLA can also reduce tumor growth in rat models (Colquhoun 2002).

Although studies in vivo or vitro have demonstrated the involvement of omega-6 fatty acids in pro-cancer or anti-cancer processes, the associations in epidemiological studies were inconsistent, showing inverse (Chavarro et al. 2007; Laaksonen et al. 2004; Rissanen et al. 2003) or positive (Harvei et al. 1997; Pot et al. 2008) associations. Kang and Liu (2013) suggested that the lack of conclusive evidence linking omega-6 to cancer risk may be because these studies only considered absolute levels of omega-6, rather than its ratio with omega-3 fatty acids. Omega-3 fatty acids compete with omega-6 for the same metabolic enzyme system, so they can limit the expression of omega-6-derived metabolites such as AA and leukotriene, and down-regulate the expression of growth factors (Kang and Liu 2013) (Fig. 3). The ratio of omega-3 to omega-6 is considered to be a predictor of cancer progression (Huerta-Yépez et al. 2016; Xu and Qian 2014). Results from European Community Multicenter Study showed that considering omega-3 or omega-6 levels in adipose tissue independently, there was almost no association with breast cancer risk, while the omega-3/omega-6 ratio displayed an inverse association with breast cancer risk (Simonsen et al. 1998). Comparing the fatty acid composition in adipose tissue in breast cancer cases and benign controls suggests that 18:3n-3/18:2n-6 and long chain omega-3/total omega-6 ratios exhibited a negative association with breast cancer (Maillard et al. 2002). Similarly, a case-control study showed a high omega-6/omega-3 diet ratio predicts the risk of prostate cancer, and possibly high-grade prostate cancer (Williams et al. 2011). A nested case-control study of Australian adults also reported that a high ratio of plasma omega-3/omage-6 concentrations was associated with a reduced risk of squamous cell carcinoma (SCC) (Wallingford et al. 2013). As such, it may be more informative to consider the ratios in the prediction of cancer risk.

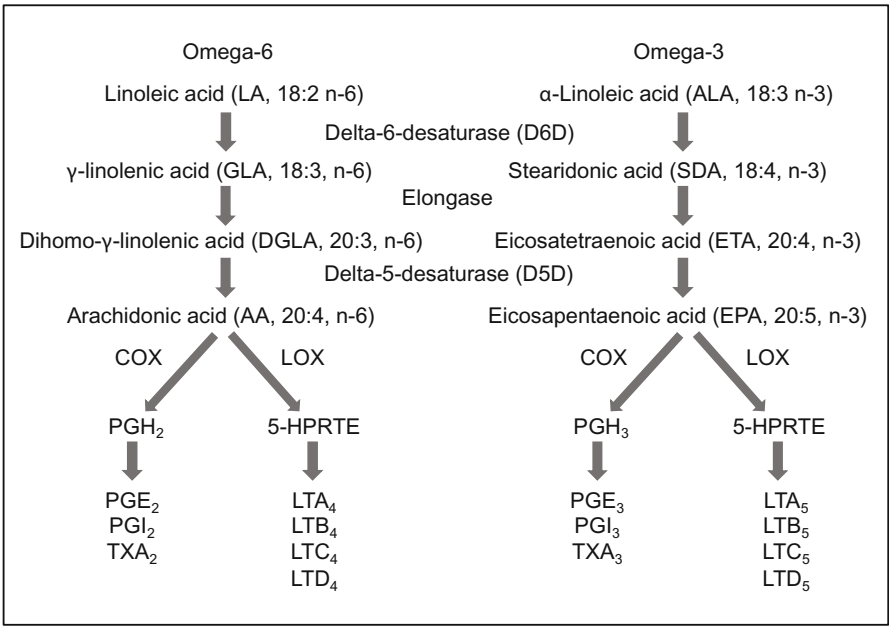

Fig. 3 Omega-6 and omega-3 fatty acid metabolism

Limitations on the Application of Omega-6 Biomarkers

Circulating or tissue fatty acids may predict dietary intake, while they are also influenced by other factors, such as smoking, alcohol drinking, BMI, physical activity and energy intake. Meanwhile, these biomarkers may not be sensitive to small amount of dietary fatty acid intake. In addition, the evaluation of omega-6 fatty acid biomarkers is usually expressed as a percentage of total fatty acids, which only reflects the relative intake of omega-6 fatty acids rather than absolute measure of total omega-6 fatty acid intake (Baylin and Campos 2006). As biomarkers for diseases, omega-6 fatty acids may predict cardiovascular disease, diabetes, asthma, autoimmune disease, and cancer, However, the associations with these diseases varied in different study designs, which needs more validation before clinical application.

Mini-Dictionary of Terms

- **Leukotrienes**. A class of eicosanoid inflammatory mediators derived from the metabolism of arachidonic acid in leukocytes, usually accompanied by the production of histamine and prostaglandins, and are important chemical mediators in Inflammation, allergies and immune diseases.

- **Mendelian Randomization study**. A method of data analysis that uses genetic variants as instrumental variables to examine the causal relationship between intermediate phenotype and disease outcomes. As the genetically determined risk factors are randomly allocated at born, MR can lower confounding bias by applying genetic variants as instruments.

Summary Points

- Omega-6 fatty acids are responsive to dietary intake and may be used in the assessment of dietary fatty acids intake in epidemiological and clinical studies.
- Omega-6 fatty acids are potential biomarkers for predicting cardiovascular disease risk.
- Omega-6 fatty acids are likely to be a marker of metabolic changes in pre-diabetes.
- Omega-6 may serve as a potential predictive biomarker for asthma.
- LA and its derivatives in omega-6 fatty acids have predictive value for autoimmune diseases such as SLE and RA.
- The ratio of omega-6 and omega-3 fatty acids may be considered as informative biomarker in the prediction of cancer risk.
- The use of omega-6 fatty acid biomarkers to assess dietary intake, and predict chronic diseases still has many limitations that prevent widespread apply in practice.

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